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Treatment of glioblastoma U-87 by systemic administration of an antisense protein kinase C-alpha phosphorothioate oligodeoxynucleotide.

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Glioblastoma multiforme is the most common form of malignant brain cancer in adults and, unfortunately, is not amenable to treatment with current therapeutic modalities. Human glioblastoma U-87 has many of the distinguishing phenotypic features of primary glioblastoma, including an autocrine form of proliferation, high levels of protein kinase C alpha (PKC alpha), and infiltration via white matter tracts. We show that treatment of mice bearing U-87 xenografts with an antisense phosphorothioate oligodeoxynucleotide (S-oligodeoxynucleotide) against the 3'-untranslated region of PKC alpha mRNA results in suppression of tumor growth. Growth was inhibited in both subcutaneous and intracranial tumors, and in the latter instance, treatment with the antisense PKC alpha S-oligodeoxynucleotide resulted in a doubling in median survival time (> 80 days), with 40% long term survivors. The antisense S-oligodeoxynucleotide did not produce systemic toxicity in mice with subcutaneous or intracranial tumors after daily intraperitoneal injection for 21 or 80 days, respectively, and a scrambled S-oligodeoxynucleotide with the same nucleotide composition as the antisense S-oligodeoxynucleotide did not produce an antitumor effect. The intratumoral levels of both antisense and scrambled S-oligodeoxynucleotide in subcutaneous tumors were 2 microM after 21 daily doses of 20 mg/kg S-oligodeoxynucleotide. The antisense S-oligodeoxynucleotide selectively reduced the levels of PKC alpha in subcutaneous tumors but not those of protein kinase C epsilon or protein kinase C zeta. This is the first demonstration that the growth of glioblastoma multiforme can be suppressed by an antisense PKC alpha S-oligodeoxynucleotide and suggests that this may represent an effective therapy for this type of malignancy.

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